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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/955,555	09/17/2001	Richard R. Bott	GC278-C3	1655

5100 7590 12/24/2003

GENENCOR INTERNATIONAL, INC.
ATTENTION: LEGAL DEPARTMENT
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EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/955,555	BOTT ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 11-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 11-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants amendment of claims 1, 13 and 16, cancellation of claims 9 and 10, in Paper of 10/14/2003, is acknowledged. Claims 1-8, 11-29 are still at issue and are present for examination.

Applicants' arguments filed on 10/14/2003 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 17-29 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 10.

Information Disclosure Statement

Applicants comments regarding the submission of the Naka reference are acknowledged.

Specification

The disclosure is objected to because of the following informalities:

The amendment filed 10/14/2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material

which is not supported by the original disclosure is as follows: SEQ ID NO: 29 of the newly submitted sequence listing comprises an additional 68 amino acids on the amino terminal end of the sequence, thus making it 599 amino acids in length compared with the sequence submitted in the original application.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Objections

Claim 1, 4 and 5 are objected to because of the following informalities:

Newly amended claim 1 recites "comprises an amino acid sequence as shown in SEQ ID NO: 29". It is suggested that this be amended to recite "comprises **the** amino acid sequence **of** [as shown in] SEQ ID NO: 29"

Claim 4 is drawn to the composition of claim 4, wherein said peptide backbone comprises scaffoldin derived from a microorganism which produces a cellulosomal or amylosomal complex. As the peptide backbone of claim 1 comprises the amino acid sequence of SEQ ID NO: 29, it comprises scaffoldin derived from a microorganism which produces a cellulosomal or amylosomal complex and thus claim 4 is duplicative of claim 1.

Similarly claim 5 is similarly duplicative of claims 4 and 1 from which it depends.

. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 and 11-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection is stated in the previous office action and repeated below for applicants convenience.

While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The term "heterologous" in claim 1 (claims 2-16 dependent from) is used by the claim to mean "two or more proteins or enzymes which are derived from taxonomically distinct organisms," while the accepted meaning is " two or more proteins or enzymes which are not normally associated with each other". For the sake of advancing prosecution the phrase is interpreted as " two or more proteins or enzymes which are not normally associated with each other".

Applicants traverse this rejection on the basis that applicants have used this term in a manner consistent with the art and applicants present two definitions taken from two references which is in agreement with applicants intended meaning.

Applicants argument is not found persuasive on the following basis. Applicants specification recites applicants intended meaning of "heterologous proteins" or "heterologous enzyme", however the phrase to which the previous rejection is based is

on the term "heterologous", within the context of "said enzyme is heterologous to said peptide backbone". Within this context the term heterologous is interpreted as previously stated, as " two or more proteins or enzymes which are not normally associated with each other". If it is applicants intent that within this context, heterologous is to have a meaning other then that previously stated, it is suggested that applicants amend the claim to specifically reflect this, such as "wherein said enzyme is derived from taxonomically distinct organism as said peptide backbone". Applicant is reminded that "heterologous" is used in the same context as discussed above in claim 15.

The rejection of claim 7 is repeated below. Claim 7 is indefinite in the recitation of "a dockerin derived from Clostridium sp. or a derivative thereof capable of non-covalently binding to said peptide backbone" as the specification fails to teach which identifying characteristics distinguish a "a derivative of a dockerin derived from *Clostridium* sp." from "dockerins" derived from other species. The application teaches that a "dockerin" means a peptide sequence which is capable of attaching in a non-covalent manner to a peptide backbone and is derived from *C. thermocellum* but does not define the structural relationship of a dockerin derived from *C. thermocellum* to a *C. thermocellum* dockerin, or how this relates to a dockerin derived from other species.

Applicants submit that the specification defines "dockerin" or "dockerin protein" as well as "derivative" and that applicant has provided the amino acid sequence of a dockerin derived from Clostridium sp. in Figure 1 and applicants thus sumize that one of skill in the art would be able, from this information to determine if a sequence is one derived from Clostridium sp. or is a derivative thereof.

Applicants argument is not found persuasive because as was previously stated, while the application teaches that a "dockerin" means a peptide sequence which is capable of attaching in a non-covalent manner to a peptide backbone and is derived from *C. thermocellum, the specification* but does not define the structural relationship of a "dockerin derived from" a *C. thermocellum* dockerin, or how such a derivative of such a *C. thermocellum* dockerin, relates to a dockerin isolated from other species.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applies to claims 1-7 and 11-16. In response to this previous rejection applicants have amended claims 1, 13 and 16 and traverse the rejection as it applies to these newly amended claims. Applicants amendment of claim 1 to include the amino acid sequence of the peptide backbone as SEQ ID NO: 29 has necessitated the withdrawal of claims 1-9 and II-13 from the rejection leaving claims 14-16. Applicants traverse the rejection as it applies to claims 14-16 as follows.

Applicants traversal of this rejection based on a lack of written description appears to be combined with applicants traversal of the claims for a lack of enablement below.

Claims 14-16 continue to be directed to a genus of compositions comprising any scaffoldin protein or any peptide backbone bound to any enzyme or any array of enzymes wherein said composition is produced recombinantly. It is noted that the current rejected claims continue to be drawn to any peptide backbone bound to any enzyme, whereas the rejected claims contain absolutely no structural limitations. As previously stated, the taught representative species of the encompassed claims are insufficient to describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-8 and 11-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-8 and 11-13 are rejected under 35 U.S.C. 112 because the newly amended recitation of the limitation that the peptide backbone comprises the amino acid

sequence of SEQ ID NO: 29 is not supported by the original specification and is thus considered new matter (See above objection to the specification).

As discussed above, SEQ ID NO: 29 of the newly submitted sequence listing comprises an additional 68 amino acids on the amino terminal end of the sequence, thus making it 599 amino acids in length compared with the sequence submitted in the original application.

Claims 14-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions of enzymes non-covalently bound to a peptide backbone, using specific peptide backbones such as those **obtained** from *Clostridium* sp. comprising the amino acid sequence as shown in SEQ ID NO: 29 and specific dockerins, such as those obtained from *Clostridium* sp, does not reasonably provide enablement for any composition comprising any peptide backbone non-covalently bound to any enzyme, nor said composition wherein said enzyme is non-covalently bound to said peptide backbone by means of a "dockerin" derivative capable of non-covalently binding to said peptide backbone. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applies to claims 1-7 and 11-16. In response to this previous rejection applicants have amended claims 1, 13

and 16 and traverse the rejection as it applies to these newly amended claims. Applicants amendment of claim 1 to include the amino acid sequence of the peptide backbone as SEQ ID NO: 29 has necessitated the withdrawal of claims 1-9 and II-13 from the rejection leaving claims 14-16. Applicants traverse the rejection as it applies to claims 14-16 as follows.

Applicants traverse this rejection on the basis that the Office action provides no extrinsic evidence regarding non-enablement, but rather merely relies upon the opinion of the examiner that the breadth of the claims are unsupportable because there aren't enough examples. Applicants further argue that the rejection is entirely devoid of technical reasoning and/or reference to extrinsic evidence which supports the position of the office that one of skill in the art would be unable to make and use the invention as claimed.

Applicants argument is not found persuasive. As previously stated, factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 14-16 continue to be directed to a genus of compositions comprising any scaffoldin protein or any peptide backbone bound to any enzyme or any array of enzymes wherein said composition is produced recombinantly. Applicants claims

contain absolutely no structural limitations such that they read on **any** peptide backbone bound to **any** enzyme. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of compositions broadly encompassed by the claims.

As previously stated, since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to teaching compositions of enzymes non-covalently bound to a peptide backbone, using specific peptide backbones such as those **obtained** from *Clostridium* sp. comprising the amino acid sequence as shown in SEQ ID NO: 29 and specific dockerins, such as those obtained from *Clostridium* sp.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to

modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any peptide backbone or dockerin protein because the specification does **not** establish: (A) regions of the these proteins structure which may be modified without effecting non-covalently binding activity; (B) the general tolerance of these proteins to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the binding activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those peptide backbones of the claimed genus having the claimed binding activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated

with the scope of the claims broadly including any number of amino acid modifications of any peptide backbone or dockerin protein. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those peptide backbones and dockerin derivatives having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 14-16 remain rejected under 35 U.S.C. 102(b) as being anticipated by Tokatlidis et al. (Protein Engineering Vol 6, No 8, pages 947-952, 1993, See IDS).

This rejection was previously stated as it previously applied to claims 1-9 and 11-16, and the rejection is repeated below.

Tokatlidis et al. teach the properties conferred on *Clostridium thermocellum* endoglucanase CelC by grafting the duplicated segment of endoglucanase CelD. Specifically Tokatlidis et al. teach a composition comprising one or more enzymes bound to a peptide backbone, CipA, wherein said enzyme is heterologous to said

peptide backbone and said backbone is capable of having bound thereto a plurality of enzymes.

In response to this previous rejection applicants have amended claims 1, 13 and 16 and traverse the rejection as it applies to these newly amended claims. Applicants amendment of claim 1 to include the amino acid sequence of the peptide backbone as SEQ ID NO: 29 has necessitated the withdrawal of claims 1-9 and II-13 from the rejection leaving claims 14-16. Applicants traverse the rejection as it applies to claims 14-16 as follows.

Applicants submit that Tokatlidis et al. merely show that two enzymes from *Clostridium thermocellum* have similar behavior when fused to a duplicating segment and that both enzymes will also bind to the scaffolding protein, which applicants submit is not terribly surprising. This seems somewhat to be somewhat contradictory to applicants comments which immediately follow, in which applicants state "it has not been established that incorporation of heterologous enzyme components into the cellulosome would be successful or that such a heterologous complex could possess enough activity to be functional". As applicants themselves stated why would it be terribly surprising as "it was clearly known that the duplicating segment would normally bind to a receptor counterpart on the scaffoldin". What difference does it make whether the enzyme is not normally associated with the scaffoldin and from the same organism or whether the enzyme is not normally associated with the scaffoldin and from a different organism?

Applicants conclude that while the disclosure of Tokatlidis et al. is relevant and important, the enzymes selected therein are NOT heterologous, i.e. the fusion protein comprises merely different components already produced by Clostridium thermocellum and that the result does not illustrate that active enzyme can be produced. This argument is not found persuasive because as stated above under the 112 second paragraph rejection, heterologous as used with in the context of claims 14 and 15, is interpreted as meaning "two or more proteins or enzymes(i.e. the peptide backbone and the associated enzyme) which are not normally associated with each other".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bayer et al. (See 892), Tokatlidis et al. (See IDS), and Gerngross et al. (See IDS).

The rejection is stated in the previous office action as it applies to claims 1-9 and 11-16.

In response to this previous rejection applicants have amended claims 1, 13 and 16 and traverse the rejection as it applies to these newly amended claims. Applicants amendment of claim 1 to include the amino acid sequence of the peptide backbone as

SEQ ID NO: 29 has necessitated the withdrawal of claims 1-9 and 11-13 from the rejection leaving claims 14-16. Applicants traverse the rejection as it applies to claims 14-16 as follows.

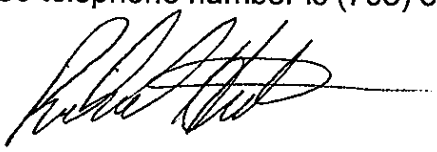
It is noted to applicants that while newly amended claims 1-9 and 11-13 drawn to a composition comprising a peptide backbone comprising the amino acid sequence of SEQ ID NO: 29 are not included in the current rejection, similar claims comprising a peptide backbone comprising the amino acid sequence of previous SEQ ID NO: 29 would be included in this rejection, as previously stated, the CipA scaffoldin protein of *Clostridium thermocellum*, discussed by Tokatlidis et al. (AN), is taught by Gerngross et al. (W) to be identical to the polypeptide backbone described by SEQ ID NO: 29 of the instant claims (See also above objection to the specification).

The remainder of applicants traversal as it applies to claims 14-16 is on the basis that neither Bayer et al. nor Tokatlidis et al. provide any credible evidence that a scaffolding protein when combined with a heterologous enzyme (as defined in the specification) (See also above 112 second paragraph rejection) would result in active protein.

As previously stated, Bayer et al. explicitly suggest "designer cellulosomes" in which a variety of different enzymes, from a variety of sources, may be incorporated into a cellulosome-like structure by several methods, including hyperactive cellulases and xylanases from **different organisms**, or recombinant organisms. Tokatlidis et al. provide evidence supporting a reasonable expectation of success, in their teaching that a recombinantly produced *Clostridium thermocellum* endoglucanase, CelC in contrast to

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
12/17/2003

wild-type CelC, was able to bind to CipA, a protein acting as a scaffolding component of the *Clostridium thermocellum* cellulase complex (cellulosome). In response to such previous statements, applicants have provided no evidence to the contrary.

Further, as Bayer et al. points out,

> One of the exciting aspects of this approach is that thousands of cellulolytic strains have already been described. A growing list of strains are already suspected of expressing cellulosomes or related entities (see Box 1), all of which will be at the disposition of the prudent biotechnologist." (page 385, column 1, paragraph 3, lines 1-6; Box 1).

The examples of cellulolytic microorganisms, other than *Clostridium thermocellum*, that appear to produce cellulosome-like multienzyme complexes taught by Bayer et al. include *C. cellobioparum, C. cellulovorans, C. cellulolyticum C. josui, Bacillus circulans, Bacteroides cellulosolvens* and *Thermomonospora curvata*. It is noted that any of the above and previously referred to enzymes isolated from this list of organisms would be encompassed by applicants definition of a "heterologous protein" or "heterologous enzyme" as discussed above.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.